REMARKS

Claim 22 has been amended to add the term "isolated." Support for this amendment can be found at, for example, page 47, lines 26-35. Claims 22-26 are presented for examination. Applicants respond below to the specific rejections raised by the Examiner in the Office Action mailed February 14, 2005. For the reasons set forth below, Applicants respectfully traverse.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO concedes that the cited utilities are credible. However, the PTO alleges that the invention lacks both substantial and specific utility.

The PTO argues there is no substantial utility for the antibodies, relying on three arguments. First, the PTO asserts that the level of overexpression in cancer cells of the nucleic acid which encodes the PRO1800 protein was minimal, and there is no evidence that overexpression is significant or a real effect and not simply produced by chance.

Second, the PTO argues that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein and antibodies and there is no evidence that the protein is overexpressed. The PTO relies on the Pennica and Konopka references to argue that even if there were a utility for the nucleic acid, there is no *necessary* correlation between the gene amplification and protein expression. The PTO concludes that because there is no *necessary* connection between the amount of DNA in a cell and the amount of mRNA, and no *necessary* connection between the level of protein in a cell and the amount of mRNA, any evidence of overexpression of one component does not provide utility for the protein.

Finally, relying on the Li, Ding and Sawiris references, the PTO argues that many genes are irrelevant in gene microarray assays, stating that "the overwhelming state of the art supports the position that many genes are irrelevant." The PTO argues that the current situation closely tracks Example 12 of the Utility Guidelines, because where there is no *necessary* relationship between the protein levels or utilities and a small level of mRNA overexpression in cancer cells, the invention lacks any "real world" context of use for PRO1800.

The PTO also argues that there is no specific utility because the protein is not associated with any disease, condition, enzymatic activity, or any other specific feature. The PTO asserts that the current situation tracks Example 4 of the utility guidelines.

Applicants respectfully disagree.

Utility – Legal Standard

As the Applicants stated in the submission filed December 22, 2004, an Applicant need only provide evidence such that it is more likely than not that a person of skill in the art would be convinced, **to a reasonable probability**, that the asserted utility is true. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The standard is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

Thus, the legal standard for demonstrating utility is a relatively low hurdle. In fact, the M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained [] because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added).

Discussion of Cited Caselaw

The PTO states that *Brenner v. Manson*, 383 U.S. 519, 534 (1966) is the starting point for analyzing utility. The PTO quotes the Court's statement that "[t]he basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." The PTO then states that "[t]here is no specific benefit, in currently available form, for the Pro-1800 protein and antibody, since there are no specific and substantial utilities for that Pro-1800 protein and antibody."

In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public"

or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

In addition, the mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "[u]sefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "to violate § 101 the claimed device must be totally incapable of achieving a useful result." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (emphasis added), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

The PTO also cites *In re Kirk*, 376 F.2d 936 (CCPA 1967), for its holding that "nebulous expressions [like] 'biological activity' or 'biological properties'" do not adequately convey how to use the claimed compounds. The PTO asserts that the instant case is identical to *Kirk.* The PTO states that the submitted Declarations provide evidence that one could determine whether the Pro-1800 protein is useful, but do not even show any utility specifically for Pro-1800.

As is explained in detail below, Applicants have asserted a utility that is far in excess of the asserted utilities in *In re Kirk.* In *Kirk*, the asserted utility for the claimed compounds was "a new class of compounds often possessing high biological activity" and "intermediates in the preparation of compounds with valuable biological properties...". *Id.* at 1120, 1121. In contrast, Applicants have offered evidence which, when considered in its entirety, establishes that it is more likely than not that the PRO1800 polypeptide is overexpressed in certain specific cancers. Applicants have asserted that this makes the claimed antibodies useful as diagnostic tools for cancer, particularly lung and colon cancer. This asserted utility clearly distinguishes this case from *In re Kirk*, and is far beyond an assertion of mere "biological activity.".

The PTO also argues that the instant case is distinguishable from *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) for two reasons. First, the PTO argues that as evidenced by the art cited by the PTO, "there is no 'reasonable certainty' that a protein will be

overexpressed when the nucleic acid is [over]expressed." Second, the PTO argues that unlike *Fujikawa* where there were *in vitro* and *in vivo* test which showed the compound lowered cholesterol, in the instant case there is no evidence that the Pro-1800 protein is diagnostic of cancer.

Applicants cited *Fujikawa* for the holding that:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

Thus, *Fujikawa* establishes that the correlation between Applicants' evidence and the asserted utility does not have to be absolute, but rather "*reasonably* indicative" such that those skilled in the art would be convinced, **to a reasonable probability**, that the utility is true. In *Fujikawa*, one of the parties relied on two articles which it claimed showed that there is no reliable relationship between *in vitro* results and *in vivo* results in cholesterol inhibiting compounds. The court rejected the articles, stating that while the articles taught that there were exceptions to the general rule, they affirmed that normally, *in vitro* results paralleled *in vivo* results. The court concluded that *in vivo* test results alone were sufficient. *Id.* at 1565-66.

Similarly in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), the court held that where "i*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween," *in vitro* testing was sufficient to establish utility. The court rejected the notion that there needed to be "an invariable exact correlation between *in vitro* test results and *in vivo* test results." *Cross v. IIzuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985).

In the instant case, Applicants have established that those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that

there is "an invariable exact correlation" between gene expression and protein expression, only that there is a reasonable correlation between the two.

As detailed below, Applicants have established that it is the normal rule that gene amplification and overexpression leads to increased protein expression. Given that general rule, Applicants' evidence of amplification and overexpression are reasonably indicative of overexpression of the encoded polypeptide. Given this evidence, those skilled in the art would be convinced, **to a reasonable probability**, that the asserted utility is true.

"Nonspecific Arguments"

Under the heading "Nonspecific Arguments," the PTO states that while Applicants have provided evidence that for some proteins, nucleic acid overexpression is correlated with protein overexpression, "there are other articles which demonstrate that there is no *necessary* relationship for *every* protein. Nonspecific arguments do not relate to PRO-1800." Office Action at 16 (emphasis added). The PTO then argues that unlike the inventors in *Fujikawa* and *Cross*, Applicants have not submitted any specific evidence of utility for the specific molecules.

Applicants respectfully submit that the holdings of the cases discussed above make the "nonspecific" evidence very relevant to the utility of the claimed invention. Applicants have cited "nonspecific" evidence to establish that there is a "reasonable probability" that when a gene is amplified or overexpressed, the protein will also be overexpressed. This is a general principle, like the general principal that *in vitro* testing of cholesterol drugs reasonably correlates to *in vivo* testing. Applicants citation of "nonspecific" evidence is therefore relevant since it establishes this general principle upon which Applicants rely. In addition, the courts have held that such general principles – that gene amplification and overexpression leads to protein overexpression – need **not** be "an invariable exact correlation" to be relied on to establish utility. Thus, contrary to the PTO's position, the fact that "there are other articles which demonstrate that there is no *necessary* relationship for *every* protein" is irrelevant – the correlation need not be "necessary," "invariable" or "exact," but merely a "reasonable" one. *See Cross*, 753 F.2d at 1050.

Turning to the assertion that unlike *Fujikawa* and *Cross*, Applicants have not submitted any specific evidence of utility for the specific molecules, Applicants respectfully disagree. As detailed below, Applicants have presented evidence of gene amplification and overexpression of the PRO1800 gene. This is specific, indirect evidence of overexpression of the protein.

Applicants emphasize that evidence of utility **can** be indirect, so long as there is a reasonable correlation between the evidence and the asserted activity. The correlation need only be a reasonable one, **not** "necessary," "invariable," or "exact."

Substantial Utility

Applicants have established that the Gene Encoding the PRO1800 Polypeptide is Amplified in Lung and Colon Tumors compared to Normal Tissue and is Useful as a Diagnostic Tool

Applicants first address the PTO's argument that the level of overexpression of nucleic acid encoding PRO1800 was minimal and insignificant. Applicants submit that the gene amplification data provided in the present application are sufficient to establish a specific and substantial utility for the gene encoding the PRO1800 polypeptide, as well as the PRO1800 polypeptide.

Applicants previously submitted the declaration of Dr. Audrey Goddard with exhibits A-G. In her declaration, Dr. Goddard states that a 2-fold increase in gene copy number, i.e., a ΔCt value of 1, is "significant and useful" in detecting cancerous tumors or the diagnosis of cancer. Goddard Declaration, paragraph 7. The gene encoding the PRO1800 polypeptide has a value of 1 or greater in several tumor samples tested, with several greater than 2 (more than four-fold amplification). Thus, the differential expression of the nucleic acid encoding PRO1800 can be used to distinguish cancerous tissue from normal tissue.

In the present Office Action, the PTO has not offered *any* reason to reject Dr. Goddard's declaration, particularly the portions relating to the reliability and significance of the evidence. Applicants remind the PTO that the applicant need **not** provide evidence such that it establishes an asserted utility "as a matter of statistical certainty." M.P.E.P. at § 2107.02, part VII (2004).

Applicants next address the PTO's argument that the art supports the conclusion that many genes are irrelevant in gene microarrays. Relying on Li, Ding, and Sawiris, the PTO concludes that "the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all." Therefore, the PTO concludes that such genes lack substantial utility as useful on gene expression arrays.

Applicants do not dispute that many genes are irrelevant when it comes to use in gene microarrays. However, the cited references do not support the PTO's conclusion that a gene

which is significantly amplified or overexpressed in certain cancer cells, such as the gene which encodes PRO1800, is not useful in a gene microarray. The cited statements from Li, that there are important and irrelevant genes and that it is useful to remove the irrelevant genes from microarrays, are statements of the obvious, and offer no support for an argument that the gene encoding PRO1800 is one of the irrelevant genes. To the contrary, Li goes on to analyze an example of a microarray used to distinguish cancerous tissue from normal tissue. (Li at 543.) The authors state that in making such a distinction, they are most interested in genes that are expressed higher in cancerous tissues than in normal tissues. (*Id.*) Thus, Li teaches that the gene encoding PRO1800 is an example of a gene that would be of interest.

Likewise, the PTO cites Ding for the proposition that genes without changes in expression profiling should be discarded as irrelevant. Regardless of the merits of the novel method disclosed in Ding, PRO1800 does show a change in expression profile between lung and colon tumors and normal tissue. Thus, nothing in Ding supports the PTO's conclusion that a gene which is significantly overexpressed in certain cancer cells, such as the gene encoding PRO1800, is not useful in a gene microarray.

Finally, the PTO cites Sawiris for the obvious statement that "[o]ne of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis." What the PTO fails to note is that the genes that were chosen for inclusion in the specialized chip were those that were either overexpressed or underexpressed in ovarian cancer. (Sawiris at 2923, second column.) Thus, contrary to the PTO's assertions, the gene encoding PRO1800 is useful for microarrays since it is overexpressed in certain colon and lung tumors.

The three references cited do not support the PTO's rejection of the asserted utility of using the gene encoding PRO1800 as a diagnostic agent for cancer. While the PTO's statement that the prior art supports the conclusion that there are many irrelevant genes is not disputed, none of the references support the conclusion that the gene encoding PRO1800 is one of those irrelevant genes when it comes to a diagnostic tool for cancer, particularly colon and lung cancer. To the contrary, the references indicate that the relevant genes are those that are overexpressed or underexpressed in the cancer of interest, genes like the one which encodes PRO1800. Thus Applicants submit that the PTO has failed to offer any support for its conclusion that the gene encoding PRO1800 is not useful as a cancer diagnostic tool. In the absence of such support, the PTO has failed to establish a *prima facie* case of lack of substantial utility.

Applicants therefore submit that using well-accepted, standard techniques, they have established that the PRO1800 gene is amplified in certain tumors, that the amplification data reported in Example 16 are significant and reliable, and the asserted utility for the PRO1800 DNA in distinguishing between normal and cancerous tissue has been established. For the reasons discussed below, this leads to utility for antibodies to the PRO1800 polypeptide as well.

Applicants have established that the Accepted Understanding in the Art is that there is a Reasonable Correlation between Gene Amplification or Overexpression and Overexpression of the Encoded Protein

Applicants next address the PTO's argument that the invention lacks utility because the overexpression of the nucleic acid is not relevant to the utility of the protein, and there is no evidence that the protein is overexpressed. The PTO cites Pennica *et al.* (Proc. Natl. Acad. Sci. (1998) 95:14717-14722) for the proposition that there is no *necessary* connection between the amount of DNA in a cell and the amount of mRNA in a cell. The PTO also cites Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) to support its position that there is no *necessary* correlation between mRNA levels and protein levels. The PTO concludes that because there is no *necessary* connection between gene amplification and mRNA, and between mRNA and protein, any evidence of overexpression of one component does not provide utility for the protein.

As discussed above, evidence of utility does not have to be to an absolute certainty, and therefore there does not need to be a *necessary* connection between gene amplification and protein expression. Rather, there need only be a *reasonable* correlation between the evidence offered and the asserted utility such that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.

The teachings in Genes V, a leading textbook in the field, illustrate that at the time the instant application was filed, it was well known by those of skill in the art that gene amplification leads to overexpression of the corresponding gene product. Benjamin Lewin, Genes V, 5th ed. 1994, pages 1196-1201, submitted herewith as Exhibit 1. In a section entitled "Insertion, translocation, or amplification may activate proto-oncogenes", the text describes various molecular events that lead to overexpression of a gene product, using the *c-myc* gene as an example. The first mechanism taught is insertion of a retrovirus upstream of the gene which

causes it to be driven by a more efficient promoter, resulting in increased mRNA and protein levels. Next, Lewin teaches that chromosomal translocations may bring a gene to a new region where it is actively expressed, resulting in increased gene and protein expression. The third mechanism whereby protein levels of oncogenes are overexpressed is gene amplification. The text emphasizes that the common thread among the different means of activation of proto-oncogenes is that the expression of the gene is increased. Thus, as of 1994, it was well-known in the art that gene amplification is correlated with overexpression of the corresponding mRNA and encoded protein.

Additional information regarding the understanding of those of skill in the art regarding the relationship between gene amplification and protein overexpression at the time the instant application was filed is found in Alitalo (Med. Biol., 62:304-317 (1984), submitted herewith as Exhibit 2), and Merlino *et al.* (J. Clin. Invest., 75:1077-1079 (1985), submitted herewith as Exhibit 3). Under the heading "Enhanced Expression of Amplified Oncogenes," Alitalo states that "[i]n **all** cases where they have been studied, the amplified oncogenes have been found abundantly expressed at the mRNA level, roughly in proportion to the amount of DNA amplification (see Table 1)." Alitalo at 313 (emphasis added). Table 1 lists eleven examples of amplified oncogenes where expression levels were examined. In all eleven cases, expression of the amplified oncogene was elevated. Thus, Alitalo clearly teaches that amplification leads to overexpression. Merlino *et al.* studied epidermoid carcinoma cells, and teach that amplification of the EGF receptor gene results in increased levels of EGF receptor mRNA and increased levels of EGF receptor protein. Taken together, the excerpt from Genes V, as well as the Alitalo and Merlino references, establish that as of the filing date of the instant application, those of skill in the art appreciated the correlation between gene amplification and overexpression of the encoded gene product.

The teachings of Genes V, Alitalo, and Merlino are confirmed in several more recent reports that also document the correlation between gene amplification and levels of protein. Applicants submit herewith two more recent studies providing evidence that the teachings referred to above are still widely accepted by those of skill in the art. Orntoft *et al.* (*Molecular and Cellular Proteomics*, 1:37-45 (2002); submitted herewith as Exhibit 4) studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene

dosage effect and teach that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts." Orntoft at 37, column 1, abstract. In addition, Hyman *et al.* (*Cancer Research*, 62:6240-6245 (2002); submitted herewith as Exhibit 5) used CGH analysis and cDNA microarrays to compare DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines. They showed that there is "evidence of a prominent global influence of copy number changes on gene expression levels." Hyman at 6244, column 1, last paragraph.

Additional supportive teachings are provided by Pollack *et al.* (*PNAS*, 99:12963-12968 (2002); submitted herewith as Exhibit 6) who studied a series of primary human breast tumors and found that "[b]y analyzing mRNA levels in parallel, we have also discovered that *changes in DNA copy number have a large, pervasive, direct effect on global gene expression patterns* in both breast cancer cell lines and tumors." Pollack at 12967 at column 1, emphasis added. Their study found that "62% of highly amplified genes show moderately or highly elevated expression, that DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." (Pollack at 12963, column 1, abstract).

Bahnassy *et al.* (BMC Gastroenterology, 4:22-34 (2004), submitted herewith as Exhibit 7) studied the amplification of *cyclin D1, cyclin A, histone H3* and *Ki-67*, and assessed the levels of the encoded proteins by immunohistochemistry. Bahnassy *et al.* found a "significant correlation between *cyclin D1* gene amplification and protein overexpression" (Bahnassy at 27, column 1). Similarly, Blancato *et al.* (British Journal of Cancer, 90(8), 1612-1619 (2004), submitted herewith as Exhibit 8), report that overexpression of *c-myc* mRNA and c-Myc protein is related to the copy number of the *c-myc* amplification (Blancato at 1613, column 2). Bahnassy and Blancato demonstrate continued evidentiary support for the widely-accepted principle that gene amplification correlates with overexpression of the encoded protein.

Together, these references collectively teach that *it is more likely than not* that gene amplification increases mRNA expression. This evidence establishes that there is a reasonable correlation between gene amplification and gene expression, and one of skill in the art would believe, to a reasonable probability, that gene amplification would lead to increased gene expression.

Relying on a single contrary example of one gene, the PTO states that the literature reports that it does not *necessarily* follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression. The PTO focuses on a statement from the abstract of Pennica that the *WISP-2* gene DNA was amplified in colon tumors, but RNA expression was reduced. Pennica at 14717. This inverse correlation is in contrast to the *WISP-1* gene, which was amplified and had higher RNA levels. The authors of Pennica offer an explanation for what they obviously viewed as an anomalous result: "Because the center of the 20q13 amplicon [of which *WISP-2* is a part] has not yet been identified, it is possible that the *apparent amplification* observed for *WISP-2* may be caused by another gene in this amplicon." *Id.* at 14722, emphasis added. Thus, the example of a lack of positive correlation between gene amplification and RNA levels relied on by the PTO may be an artifact. The fact that the authors attempt to explain this anomaly only supports Applicants' argument that the accepted understanding in the art is that there is a direct correlation between gene amplification and an increase in gene expression.

As stated above, the standard for utility is <u>not</u> absolute or even statistical certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Even if Pennica supported the PTO's argument, which it does not, one contrary example is not sufficient to prove that a person of skill in the art would have a reasonable doubt that gene amplification is correlated to gene expression. Given the evidence provided by the Applicants which establishes that there is a reasonable correlation between gene amplification and mRNA expression, one of skill in the art would believe, to a reasonable probability, that the reported amplification of the PRO1800 gene would lead to an increase in the level of PRO1800 mRNA.

Applicants next address the PTO's argument that there is no *necessary* correlation between mRNA levels and protein levels.

The PTO cites Konopka for the statement that "Protein expression is not related to amplification of the abl gene but to variation in the level of the bcr-abl mRNA produced from a single Ph1 template." From this statement, the PTO concludes that even if there is a gene amplification, that would provide no utility whatsoever for the protein or antibody, since the gene amplification does not <u>*necessarily*</u> relate to the expression information of the protein and cognate antibody." Office Action at 5 (emphasis added).

Setting aside the fact that a "necessary" correlation is not required, a reading of the entire Konopka reference reveals that it does not support the PTO's argument that there is no correlation between nucleic acid levels and protein expression. In fact, the results presented in Konopka actually present strong evidence in support of Applicants' position that there is a general understanding in the art that levels of mRNA correlate with levels of the corresponding proteins. Konopka reports on the expression of the translocated *c-abl* oncogene, known as the Philadelphia chromosome, or Ph^1. (Konopka at 4049.) In the cancer cells studied, the Ph^1 translocation creates a chimeric *abl* gene, *bcr-abl*, that encodes a structurally altered form of the *abl* oncogene product, known as $P210^{c\text{-}abl}$. As Konopka reports, "the 8-kb mRNA that encodes $P210^{c\text{-}abl}$ was detected at 10-fold higher level in [cell type A] than in [cell type B], **which correlated with the relative level of $P210^{c\text{-}abl}$ detected in each cell line.**" (*Id.* at 4050). Thus, as Applicants have asserted is most usually the case, the level of protein was correlated with the level of mRNA. Not surprisingly, as the abstract reports, the level of protein expression of $P210^{c\text{-}abl}$ is not related to the amplification of the unaltered *abl* gene, but instead correlates to the level of mRNA for the chimeric *bcr-abl* gene, which is the product of the translocation Ph^1. Konopka thus concludes, "these combined data suggest that differential bcr-abl mRNA expression from a single gene template is responsible for the variable levels of P210c-abl [the protein of interest] detected." *Id.*, p. 4051. Thus, far from supporting the PTO's assertion that it is not the norm that increased transcription leads to increased levels of the corresponding protein, Konopka strongly supports the opposite proposition asserted by Applicants – that the level of mRNA, more often than not, correlates with the level of the corresponding protein. Thus the PTO's reliance on the abstract to support their argument that there is no correlation between nucleic acid levels and protein expression is misplaced.

In further support of Applicants' assertion that changes in gene expression lead to corresponding changes in protein expression, Applicants have previously submitted a copy of a Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be overexpressed." Similarly, the previously submitted declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology states that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Polakis Declaration, paragraph 6. He cites as supporting evidence not only his years of personal experience, but also results from experiments related to the present application. He reports that for the mRNAs overexpressed in cancer that have been examined, 80% had correspondingly higher levels of the encoded protein. Polakis Declaration at paragraphs 4 and 5.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 9) and (4th ed. 2002) (submitted herewith as Exhibit 10)). Figure 9-2 of Exhibit 9 shows the steps at which eucarotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 9 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 9 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 9 at 453 (emphasis added). Thus, as established in Exhibit 1, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 10, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 10 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 10 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 10 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 2 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 11) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of

RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 12. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Exhibit 12 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 12 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 12 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 13, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Finally, Applicants submit the Declaration of Victoria Smith, Ph.D., an expert in the field of Molecular Biology, originally submitted in the related and co-pending application Serial No. 9/866,034 (submitted herewith as Exhibit 14). Dr. Smith states that Exhibit B of her Declaration reports the results of the microarray analysis conducted on the gene encoding PRO1800 (DNA35672) as part of the investigation of several newly discovered DNA sequences. The results indicate that the gene encoding PRO1800 is significantly overexpressed in nine of the eighty lung tumor samples tested compared to the normal lung tissue controls. That is the

equivalent of one in every nine samples (11%). In contrast, none of the individual normal lung tissue samples show significant overexpression of the PRO1800 gene. In addition, the average ratio of the lung tumor samples is significantly different form the average ratio of the individual normal lung tumor samples ($p<0.01$).

Dr. Smith states that "[i]t is well-established in the art that overexpression of the mRNA for a gene is likely to lead to overexpression of the corresponding protein." Smith Declaration at paragraph 6. She explain that:

> While not every lung tumor sample tested shows overexpression of the PRO1800 gene, the data in Exhibit B indicate that a significant portion of lung tumors do (one in every nine), while none of the normal lung tissue samples show overexpression. Given the known correlation between overexpression of a gene and the corresponding overexpression of the encoded protein, it is very likely that a similar number of lung tumors will overexpress the PRO1800 protein, while normal lung tissue samples will not. Together with the data reported in Example 16 that the gene encoding PRO1800 is amplified in some lung tumors, the results reported in Exhibit B indicate that the PRO1800 gene and protein, as well as antibodies to the encoded protein, can be used to differentiate some cancerous lung tissue from normal lung tissue. Smith Declaration at paragraph 7 (emphasis in original).

Because not all lung tumors show overexpression of PRO1800, it cannot be used to exclude a sample being tested as non-cancerous. However, the PRO1800 gene, protein, and corresponding antibodies are useful as a diagnostic tool for lung cancer, alone or in combination with other tools, since a significant number of lung tumors overexpress the gene and most likely the encoded protein, while no normal lung samples do.

Together, the declarations of Grimaldi, Polakis, and Smith, the accompanying references and data, and the excerpts and references provided above all establish that the accepted understanding in the art is that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. Applicants have provided microarray data showing the increased expression of the gene encoding PRO1800 in a significant portion of lung tumors, and have established that there is a reasonable correlation between expression of the gene and the level of PRO1800 protein.

The Instant Case is Similar to the Caveat in Example 12 of the Utility Guidelines

In Example 12 of the Utility Guidelines, the specification discloses a protein, receptor A, which is the binding partner for protein X. The specification does not characterize the isolated protein with regard to its biological function or any disease or body condition that is associated with the isolated protein. In addition, the function of protein X has also not been identified. One of the asserted utilities for receptor A is making monoclonal antibodies to receptor A which can be used as a therapeutic drug to effect control over the receptor. In the analysis of this asserted utility for receptor A, the Utility Guidelines state that "since neither the specification nor the art of record disclose *any* diseases or conditions associated with receptor A, the asserted utility in this case essentially is a method of treating an unspecified, undisclosed disease or condition, which does not define a 'real world' context of use." Utility Guidelines at 66, emphasis added.

The situation in Example 12 is not the situation here. Applicants have demonstrated that the nucleic acid encoding PRO1800 is amplified and overexpressed in at least lung cancer. Thus, unlike the protein in Example 12, PRO1800 **is** associated with a known disease or condition – more specifically, lung cancer.

The present situation closely resembles the caveat discussed at the end of Example 12, where receptor A is shown to be present on the cell membranes of melanoma cells but not on the cell membranes of normal skin cells. The Utility Guidelines state that in that situation, "making a monoclonal antibody to receptor A for diagnosing melanoma would constitute a well-established utility." Utility Guidelines at 70. Similarly, here Applicants have provided evidence that it is more likely than not that the PRO1800 polypeptide is expressed at higher levels in certain cancer cells than normal tissue, including additional microarray data showing that the PRO1800 gene is overexpressed in certain tumors. Because the PRO1800 polypeptide is overexpressed in certain tumors, it can be used to make diagnostic antibodies.

Specific Utility

The PTO argues that even if substantial utility were found, there is no specific utility given for antibodies to the PRO1800 protein, since antibodies to the protein, as distinguished from the nucleic acid, have not been associated with any disease, condition, or any other specific feature. The PTO argues that the a general statement of diagnostic utility, "such as diagnosing an

unspecified disease" is insufficient, and here there is no disclosure of any condition which can be diagnosed. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01, part I (2004). Applicants submit that the evidence of amplification and overexpression of PRO1800 nucleic acids in certain types of cancer cells along with the declarations and references discussed above provide a specific utility for the claimed antibodies. As stated above, Applicants have established a reasonable correlation between gene amplification, gene expression, and protein expression. This makes antibodies to the PRO1800 protein useful in diagnosing lung and colon cancer. This is not a general utility that would apply to the broad class of antibodies.

The amplification and overexpression of PRO1800 nucleic acid in certain cancer cells distinguishes this case from Example 4 of the Utility Guidelines cited by the PTO. In that example, there is no description of the protein beyond its sequence or its binding of an unidentified ligand. Here, the disclosed proteins are encoded by a nucleic acid that is amplified and overexpressed in lung cancer cells, which is reasonably correlated to overexpression of the PRO1800 polypeptide. This makes the utility of using antibodies to the protein to diagnose lung cancer specific, since in general, antibodies are not specific to proteins that are overexpressed in cancer cells, more particularly lung cancer.

The PTO's previous response to Applicants' arguments regarding specific utility is lacking. The PTO asserts that because Applicants' arguments presume the PRO1800 protein is overexpressed, and this is not *necessarily* the case, this cannot serve as the foundation to support specific utility. Howevêr, utility need not be established "beyond a reasonable doubt" or to a "statistical certainty." Rather, Applicants need only establish that the asserted utility is "more likely than not." M.P.E.P. at § 2107.02, part VII (2004). Thus, it need not be shown that overexpression of PRO1800 polypeptide is *necessarily* the case, only that it is more likely than not, which Applicants have done.

Conclusion

Given the totality of the evidence provided, Applicants submit that they have established a credible, substantial, and specific utility for the claimed antibodies as diagnostic tools.

According to the M.P.E.P. and case law cited above, irrefutable proof of a claimed utility is **not** required. Rather, a specific and substantial credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants have offered sufficient evidence to establish that there is a reasonable correlation between gene amplification, gene expression, and protein expression. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only <u>partially</u> successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was <u>wholly</u> inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that based on the gene amplification and gene expression data submitted herewith for the PRO1800 gene, the PRO1800 protein is overexpressed in lung and colon cancers, and therefore antibodies to PRO1800 have utility as a diagnostic tool for these cancers. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO rejected Claims 22-27 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. The PTO cites *In re Wands* and the factors set forth therein to determine the scope of enablement. However, Applicants respectfully submit that the PTO's conclusions are inconsistent with the teachings of *Wands*, as they rest on the erroneous assumption that a *necessary* connection between gene amplification and protein expression is required. The PTO bases its enablement rejections on the same references and arguments cited in its utility rejection under 35 U.S.C. § 101.

The Applicants believe that the evidence, declarations, references, and arguments discussed above make clear that Applicants have established that it is more likely than not that one of skill in the art would be convinced, to a reasonable probability, that the PRO1800 protein is overexpressed in certain cancers, and therefore antibodies to PRO1800 have utility as a diagnostic tool. To the extent that the enablement rejection is based on the same arguments as the utility rejection, Applicants respectfully submit that these arguments fail.

In addition, Applicants respectfully submit that the PTO has mischaracterized several key *Wand* factors. For example, under "Quantity of Experimentation," the PTO states that it would require "significant study to identify the actual function of the PRO1800 protein" requiring "years of inventive effort." Office Action at 8. Applicants submit that the function of the PRO1800 protein is not relevant to the use of the claimed antibodies as diagnostic tools for cancer – one does not need to know the role of PRO1800 in cancer to use it as a marker. The PTO makes a similar argument with regard to the unpredictability of the art, arguing that "[t]he art is extremely unpredictable with regard to protein function." The PTO then proceeds to repeat the failed arguments discussed above for the utility rejection.

Under "Working Examples," the PTO ignores the declaration of Dr. Goddard which establishes that the experiments reported in Example 18 were conducted using accepted and established methods, and that the results are significant. Likewise, the "Guidance in the Specification" ignores the disclosure of how to make antibodies, as well as how to use them as diagnostic tools, for example at page 98, lines 5-18 of the specification.

As amended, the pending claims are related to an antibody that specifically binds to the polypeptide of SEQ ID NO:2. Applicants submit that the claimed antibodies are enabled, as one

of skill in the art would know how to make and use them. The techniques for the creation of antibodies are well known and routine in the art, and the use of antibodies as diagnostic tools is also well-known in the art and disclosed in the application. Thus, at least one use of antibodies to the PRO1800 polypeptide is adequately enabled, which is all that is required – "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." M.P.E.P. 2164.01(c). In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 13, 2005

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